

- B. the 5' and 3' termini of the core strand have one or more of the following features:
- the terminal base on the 5' is a 2'-F, 2'-O-methyl, or other modified base that resists nuclease cleavage;
 - the terminal base on the 3' is a 2'-F, 2'-O-methyl, or other modified base that resists nuclease cleavage;
 - the three terminal bases on the 5' have the pattern MRM, where M is a modified base (2'-O-methyl, 2'-F), and R is an RNA base;
 - the three terminal bases on the 3' have the pattern MRM, where M is a modified base (2'-O-methyl, 2'-F), and R is an RNA base;
 - the three terminal bases on the 3' and 5' do not have consecutive PS backbone modifications;
 - the portions of the core strand that are base-paired with the sensor strand have an alternating chemical modification pattern (MR)_n;
 - the above where M is a chemically modified base that does not decrease T_m of the duplex when compared to the equivalent RNA base;
 - any combination where both the 5' and the 3' ends of the core strand have at least one of the features from a-g; and
 - the 3' and 5' regions of the core strand that are base-paired with the sensor strand are:
 - entirely made out of the pattern (M)_n, where M is a 2'-O-methyl or 2'-F modified base, or
 - at least 50% of the bases in this area are 2'-O-methyl or 2' F, and,
- up to 30%, 50%, 80% or 100% of the backbone connections are not phosphorothioate;
- C. a core strand where the three bases base-paired with 3' terminus of the guide strand have one or more of the following features:
- A M*+*M pattern, where M is a 2' modified base (eg 2'-O-methyl or 2'-F), * is a PS backbone connection, and + is an LNA base or other 2'-4' bridged base;
 - A M*+*+ pattern, as defined above;
 - A +*+*+ pattern;
 - A R*+*M pattern, where R is an RNA base;
 - A R*+*+ pattern;
 - A +*M*M pattern; and
 - the patterns in a-f, where * can be either a PS backbone connection or an unmodified (phosphodiester) backbone connection; and

- D. a guide strand with one or more of the following features:
- 30% to 95% of the bases are chemically modified bases (2'-O-methyl, 2'-F, LNA, 2'-4' bridged bases);
 - where the two terminal bases on the 5' are chemically modified;
 - where the two terminal bases on the 5' have at least one LNA
 - where the two terminal bases on the 5' are connected by a PS backbone;
 - where the two terminal bases on the 3' are both chemically modified;
 - where ~5% to 50% of backbone connections are PS; and
 - where the bases flanking the indicated site of Dicer cleavage are not chemically modified.
4. The Cond-siRNA construct of claim 1, wherein the duplex domain of the sensor strand has LNA modification, 2'-O-methyl modification, or both.
5. The Cond-siRNA construct of claim 1, wherein the duplex domain of the sensor strand does not have phosphorothioate (PS) modifications.
6. The Cond-siRNA construct of claim 1, wherein either or both termini of the core strand are modified with either PS or 2'-O-methyl.
7. The Cond-siRNA construct of claim 3, wherein the chemical modifications are in the toehold domain, including LNA modification, 2'-O-methyl modification, PS modification, or a combination thereof.
8. The Cond-siRNA construct of claim 1, wherein the sensor duplex is 23 bp, and the RNAi duplex is 23 bp.
9. A method of activating a synthetic RNAi comprising administering the Cond-siRNA construct of claim 1 to a subject, wherein an input strand binds to the sensor strand causing displacement of the sensor strand from the Cond-siRNA, thereby to activate the RNAi in the Cond-siRNA construct.
10. The method of claim 9, wherein the input strand is a cellular RNA transcript.
11. A method of treating a disease or condition, comprising administering the Cond-siRNA construct of claim 1 to a subject in need thereof, wherein an input strand binds to the sensor strand causing displacement of the sensor strand from the Cond-siRNA, thereby to activate the RNAi in the Cond-siRNA construct, and wherein the RNAi targets the disease or the condition.
12. The method of claim 11, wherein the input strand is a cellular RNA transcript.

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